Biological Psychiatry: Celebrating 50 Years

# Commentary

# Role of Kappa Opioid Receptors in Symptoms of Schizophrenia: What Is the Neurobiology?

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The opioid peptide–containing neurons comprise a neuromodulatory system that is widespread across the central nervous system with three classical cognate receptors (mu, delta, and kappa subtypes), all with their preferred endogenous peptide ligands. The kappa opioid receptors (KORs) have the strongest affinity for the endogenous ligand dynorphin (1) and demonstrate specific distribution patterns, concentrated along the spinal nociceptive pathways, brainstem, striatum, subcortical limbic regions, and cortex. They regulate a broad set of central nervous system functions, including nociception, reward, anxiety, motivation, and cognition, and are therefore likely to have significant roles in several neuropsychiatric disorders. Not surprisingly, KORs have been implicated in chronic pain, addictions, anxiety, and depression, all of which have been reviewed extensively in many previous publications (2,3). These receptors have also been implicated in psychotic disorders, and the article by Clark and Abi-Dargham (4) in this issue of *Biological Psychiatry* provides a comprehensive review of the evidence supporting the role of KORs in schizophrenia.

Recognition of the unique role of KORs in eliciting psychiatric symptoms dates back nearly 40 years, when KOR selective agonists such as cyclazocine were developed as analgesics with a lower potential for addiction. While these compounds were indeed potent analgesics, they also resulted in significant dysphoria and other psychotomimetic effects, implicating the role of KORs in psychiatric symptoms such as depression and low motivation states. Thus, early efforts to develop selective KOR agonists as analgesics were abandoned primarily owing to their neuropsychiatric side effects. However, because these agonists were so potent in inducing anxiety, depression, low motivation states, and even some symptoms of schizophrenia, there is renewed interest in studying KOR antagonists as potential therapeutics for these psychiatric syndromes. More recently, salvinorin A, a chemical agent derived from the plant *Salvia divinorum* ("magic mint"), which has long been noted to induce hallucinations and dissociative mental states similar to positive symptoms of schizophrenia when administered to healthy volunteers, was identified as being a potent and selective KOR agonist (5). These data points add up to an emerging view that activation of kappa receptors may be critically involved in eliciting a variety of neuropsychiatric symptoms, such as dysphoria, lack of motivation, social withdrawal, cognitive functions, and hallucinations. In the context of a complex disorder like schizophrenia characterized by negative symptoms (low motivation and social withdrawal), cognitive symptoms (poor attention and working memory), and positive symptoms (hallucinations and delusions)—all of which could be induced by KOR agonists in otherwise psychiatrically healthy volunteers—makes this receptor a target of high interest to consider for novel therapeutic approaches.

As reviewed by Clark and Abi-Dargham (4), numerous trials have been conducted with nonselective opioid antagonists in patients with schizophrenia. Many of these were small studies with inadequate power that often used subtherapeutic doses of antagonists to adequately engage central KORs. Despite these limitations, studies have been consistent in supporting the idea that even nonselective opiate receptor antagonists are likely to improve some of the negative and cognitive symptoms seen in schizophrenia. Few such trials have even reported benefits of improving positive symptoms, especially when high doses of these nonselective opioid antagonists were used. Clark and Abi-Dargham's conclusion (4), after a thorough review of the existing literature, is that clinical trials of selective KOR antagonists in schizophrenia would be highly desirable. The hypothesis that a selective KOR antagonist is likely to yield more robust improvements in schizophrenia—certainly more than what is reported with nonselective opioid antagonists, particularly in the negative and cognitive symptoms—is justified by the clinical literature and also supported by extensive preclinical studies.

In addition to their therapeutic potential, these data also raise the question of what role the KORs play in the pathophysiology of schizophrenia. Results from the few published human studies or postmortem brain tissues from patients with schizophrenia and other psychotic illnesses have been mixed. While some studies have reported abnormal dynorphin levels in the cerebrospinal fluid of patients or KORs in postmortem bran tissues, there have also been several studies that have failed to replicate these findings (4). These mixed results are not surprising, given the many methodological differences and heterogeneous patient samples in these relatively small and often underpowered studies. In contrast to such limited information from human subjects with schizophrenia, there is a strong body of preclinical and neurobiological data regarding KORs eliciting some of the symptoms observed in patients with schizophrenia and other neuropsychiatric disorders.

The strongest preclinical case can be made for the role of KORs in the negative and cognitive symptom domains of schizophrenia. There are many similarities between the potential circuits that aberrant KOR function may modulate to cause negative symptoms of schizophrenia and with other negative emotional states, such as depression and dysphoric states during drug withdrawal [see (3) for review]. The nucleus accumbens (NAc) is a key structure that regulates reward and

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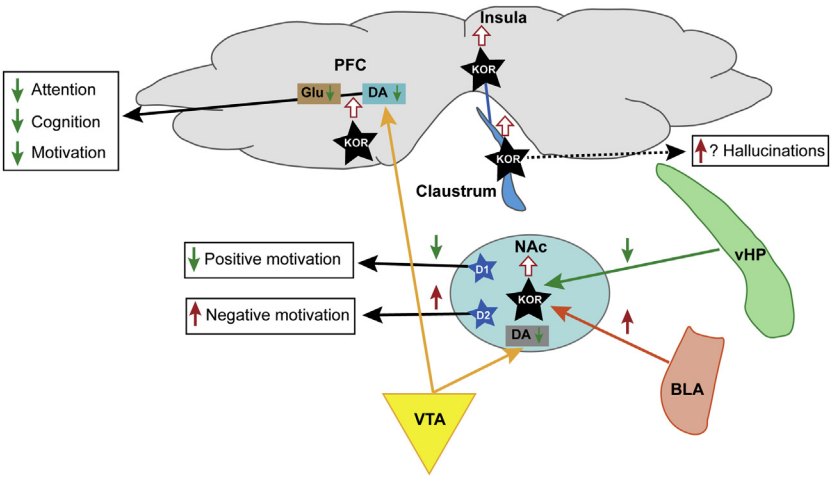


**Figure 1.** Putative networks for symptom domains of schizophrenia regulated by kappa opioid receptors (KOR). Increased kappa activation in the nucleus accumbens (NAc) enhances glutamatergic input from the basolateral amygdala (BLA) and reduces the glutamatergic input from the ventral hippocampus (vHP), reduces dopamine (DA) release from the ventral tegmental area (VTA), and results in biasing the output of the NAc toward $D_2$ receptor–positive medium spiny neurons vs. $D_1$ receptor–positive medium spiny neurons. This results in reduced reward-oriented responses and reduced motivated behaviors. Regarding cognitive symptoms, KOR activation in the prefrontal cortex (PFC) results in reduced glutamate (Glu) and DA release, leading to poor attention and cognitive performance. Finally, it is suggested that KOR activation within a putative salience network (centered around the cingulate cortex, striatum, and its connections) and the claustrum, a unique sensory integration area with one of the highest densities of KORs, would be capable of eliciting hallucinations and other positive symptoms. (Figure preparation assisted by Dr. Andrei Molosh.)

motivated behaviors, and KORs play a complex role in modulating the internal network dynamics and biasing the output of this region (6). The two major populations of output neurons within the NAc are the $D_1$ receptor– and $D_2$ receptor–positive medium spiny neurons (D1- and D2-MSNs, respectively). D1-MSNs are critical for reward and positively motivated behaviors, and D2-MSNs regulate aversive and negative behavioral states. Dopamine input from the ventral tegmental dopaminergic neurons to the MSNs is a critical driver for these motivational behaviors. Contextual versus anxiety/emotional salience input is provided to this MSN network by glutamatergic neurons from the ventral hippocampus or basolateral amygdala, respectively. Activation of KORs within the NAc appears to selectively enhance the glutamatergic input from the basolateral amygdala while reducing the input from the ventral hippocampus, as well as reducing the overall dopamine neurotransmission within NAc. The sum of these complex network effects is that there is a significant increase in the D2-MSN output with a decrease in D1-MSN output (Figure 1). At the whole-animal level, this results in an enhanced state of negative motivation, decreased interest in rewarding behaviors, and social withdrawal, providing a neurobiological mechanistic model for the development of negative symptoms of schizophrenia.

The putative mechanistic model for KORs modulation of cognitive functions, especially attention and choice behaviors, is also based on strong preclinical data. Activation of KORs with salvinorin A shows acute disruption of attention and task performance similar to an acute dose of ketamine, supporting a common acute symptomatic effect of both of these psychotomimetic agents on cognition (7). More specifically, activation of KORs significantly reduces dopamine and glutamate release within the prefrontal cortex, two neurochemical mechanisms that are critical for appropriate attention to salient stimuli and goal-directed task performance (8). Therefore, activation of KORs across a broad network of prefrontal cortex circuits could decrease attentional processes and performance efficiency of cognitive tasks, symptoms that are frequently seen in schizophrenia (Figure 1). If this is the case, it is likely that treatment with a KOR antagonist would improve these deficits.

The mechanisms by which activation of KORs results in hallucinations, dissociative states, or perceptual disturbances similar to positive symptoms of schizophrenia is less clear at this time. These sensory perceptual disruptions are more difficult to model in preclinical studies, and thus mechanistic circuits cannot be easily developed based on animal experiments. The source of the dissociative/hallucinogenic effects of the early drugs (e.g., cyclazocine) was further confounded by misunderstanding their mechanism of action as being antagonism of sigma receptors (later clarified to be *N*-methyl-D-aspartate receptors) versus partial agonism at KORs. Multiple recent human studies have demonstrated that positive symptoms can be robustly elicited by selective KOR agonists such as salvinorin A. As reviewed by Clark and Abi-Dargham (4), several somewhat complicated theories have been proposed to explain this effect, but most lack any supportive evidence. Elucidation of this effect will likely require more detailed human imaging studies and an understanding of the neurobiologically relevant circuits for the development of positive symptoms. In this context, the more recent imaging studies of acute hallucinations in patients with first-episode psychosis that have identified some key components of the salience network (e.g., cingulate cortex) and the claustrum as a putative network for hallucinations in schizophrenia are important (9). Within this network, the claustrum is a particularly interesting site because it has been implicated in multimodal sensory integration, attention, and consciousness and because it has one of highest densities of KORs (10). It is intriguing to speculate whether aberrant activation of KORs in the claustrum–cingulate network with agonists such as salvinorin A might be a mechanism by which these compounds elicit their hallucinogenic effects (Figure 1).

In summary, there is a preponderance of preclinical and some encouraging human evidence summarized in the article by Clark and Abi-Dargham (4) that supports the idea that aberrant activity of KORs may be involved in the expression of some core symptoms from all three symptom domains of schizophrenia. Therefore, clinical studies of selective KOR

antagonists with appropriate pharmacokinetic properties in patients with schizophrenia may be fruitful in developing symptom-specific therapies to improve daily functioning in subjects who are disabled by this severe psychiatric illness.

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AS is the cofounder of the Indiana University startup company Anagin, which is unrelated to the content of this commentary.

## Article Information

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